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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	33

DATE MAILED: 08/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/202,047	ITOH ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,7,9 and 12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,7,9 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 16-17 have been canceled.

Claims 6 and 7 have been amended.

Claims 6-7, 9 and 12 are under examination.

2. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

3. The following Office Action contains some NEW GROUNDS of rejections.

Rejections Withdrawn

4. The rejection of claims 6-7, 9, 12, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in view of the new ground of rejection.

Response to Arguments

5. The rejection of claims 6-7, 9, 12, under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial asserted utility or a well established utility is maintained.

The response filed 6/16/03has been carefully considured but is deemed not to be persuasive. The response states it is art known that a term tumor antigen means a

target of CTLs and the references of Bruggen et al discloses this and the protein of the present invention is known in the prior art as a tumor antigen protein and cites two references (see page 6 of response) and the specific utility of SART-1, the protein of the invention, is described on page 24-25 of the specification and the reference of Yamana et al describes the trial with SART-1 derived peptides as vaccines (see page 7 of response). In response to these arguments, while it is known what a tumor antigen is, the specification contemplates the utility in a method of administration as a vaccine (see pages 24-25). The specification discloses that the mRNA for the tumor antigen protein gene was present in various cancer cell lines and normal tissues (see Figure 1 and page 32). Thus there is no differential expression of the claimed protein or peptides in any tissue. In addition, Rosenberg et al, (Exhibit 3 supplied with response) states that SART-1 is also expressed in normal proliferating cell lines (see page 283, right column). In addition, the art of Yamana et al is not persuasive because the reference is only in English for the abstract and in the abstract it states that the phase I trial is in vitro and only works in some cases and it is not clear from the abstract what cases or conditions were studied. Thus, the asserted utility is not specific because the protein or peptides are expressed in normal and cancerous and the vaccine would not be specific for cancerous cells and there is no indication that the peptides can be used as a vaccine invivo.

Therefore, for the reasons stated above, the claimed invention of polypeptides and compositions containing said polypeptides is not supported by a specific utility.

6. The rejection of claims 6-7, 9, 12, rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention is maintained.

The following is a NEW GROUND of rejection

7. Claims 6-7, 9, 12, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a tumor antigen and peptides of such that the peptides bind HMC I antigen and are recognized by CTLs. The specification discloses SEQ ID NO:2 and peptides from SEQ ID NO:2. The specification discloses that mRNA of the gene for the tumor antigen is expressed in various cancer lines and in normal

tissues (see Figure 1). The specification speculates that the protein and peptides are used for a vaccine.

The specification provides no exemplification of or guidance on how to use the claimed vaccine formulation or peptides for activity immunotherapy in humans. The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1).

Furthermore, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence

suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). The specification does not demonstrate that the expression of these peptides has resulted in autoantibodies against the antigen thus it would be highly unpredictable that administration of the antigen as a cancer vaccine, would lead to an effective immune response against the tumor.

The specification also contemplates using the DNA which encodes the antigen as a cancer vaccine wherein the peptides are expressed (see pages 13-14 of the specification). However, one cannot extrapolate the teachings of the specification to the scope of the claims because the specification provides no exemplification of or guidance on how to use pharmacuetical compositions of DNA or protein (i.e. DNA vaccineor vaccine) for immunization purposes with any predictability. With regards to tumor immunotherapy, the goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, gene therapy against tumors is highly unpredictable as underscored by Crystal, R.G. (Science, Vol. 270, October 1995, pages 404-410) who teaches that in tumor vaccine studies intended to evoke a tumor-directed immune response, there is no convicining evidence (other than anecdotal case reports) that tumors actually regress, despite the promising observations in experimental animals. In other words, humans are not simply large mice (page 409, 1st column). More recently, Tait *et al.* (Clin.Canc.Res., Vol. 5, July 1999, pages 1708-1714) revealed just how unpredictable gene therapy was in the clinical setting. The authors' prior phase I trial of 12 patients with extensive ovarian cancer treated with a retroviral vector expressing the BRCA1 splice variant (LXSN-BRCA1sv)

demonsrated vector stability, minimal immune response, gene transfer and expression, and some tumor reduction in the patients (page 1708, 2nd column, 2nd paragraph). In contrast, the Phase II trial inititiated in pateints with stage III and IV grade ovarian cancer, showed a high preponderance for vector instability (vector was degraded rapidly), a rapid immunological response invoking neutralizing antibodies to the retroviral vector, and no clinical response to the therapy. Although the difference in response to the therapy may be attributed to differences in immunocompetence between the phase I and II patients (page 1712, 2nd column), the end result seems to indicate that further experimentation is necessary prior to the successful application of DNA vaccines, especially with the regards to cancer therapy.

Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable for of skill in the art to use the compositions or vaccine formulations as contemplated in the disclosure. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

The response filed 6/16/03 has been carefully considured but is deemed not to be persuasive. The response states that START-1 peptide vaccine has recently been used as a peptide vaccine in clinical trials and the response summarizes the Wands factors and states that the instant invention provides a peptide or protein with a sequence and activity and the skill in the art is high and the specification provides guidance on whether the peptide has the activity claimed and the specification provides examples of the prep of the protein and an assay to determine the activity (see pages 10-11). In response to these arguments, the arguments related to the art of Yamana et al directed to phase I trials above can be stated here. With regard to the Wands factors, while one may be able to make a peptide with the claimed properties and screen for those properties, the specification contemplates using the DNA as well as the protein as a vaccine and as stated above in the 112 first rejection it would require undue experimentation to practice the claimed invention.

Summary

8. No claims are allowed

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

10. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

LARRY R. HELMS, PH.D
PRIMARY EXAMINER